## II. REMARKS

The presently claimed application is directed to a method for treating a medical condition caused by excessive growth of non-cancer cells, specifically psoriasis, with an EGFR/HER1 antagonist.

### A. Amendments

In the interests of advancing prosecution of the present invention, Applicant has amended claims 1-3, cancelled claims 6-7, and added new claim 8. Claim 1 has been amended to specify that the hyper-proliferative disease stimulated by a ligand of a member of the EGF family of receptors is psoriasis, which was originally set forth in dependent claim 7, now cancelled without prejudice. Claim 1 has also been amended to recite systemic administration (see Specification, p. 13, ll. 4-28). Finally, Claim 1 has been amended to specifically claim one member of the EGF family of receptors, namely EGFR or HER1, as originally set forth in dependent claim 2. Dependent claim 8 has been added to recite a defective receptor, which was set forth in claim 1 originally. Accordingly, no new matter has been added.

Attached hereto are a copy of a version of the amendments with markings to show the changes made and, for the convenience of the Examiner, a copy of the pending claims upon entry of the present amendments.

### B. Outstanding Office Action

In the Office Action dated October 29, 2002, claims 1-7 have been rejected under 35 U.S.C. § 112, ¶ 1 and 35 U.S.C § 103(a).

#### 1. Rejection under 35 U.S.C. § 112, ¶1

The Office alleges that the Applicant fails to broadly enable administration of an antagonist of the EGF family for treatment of hyper-proliferative diseases stimulated by a

ligand of a member of the EGF family of receptors. The Office, however, concedes that the Applicant has enabled the treatment of psoriasis using the chimeric monoclonal antibody C225. In the interest of advancing prosecution, claim 1 has been amended to specifically claim the use of an EGFR/HER1 antagonist for treating psoriasis. As such, Applicant respectfully submits that the present rejection is moot. Alternatively, in the event that the Office maintains the enablement rejection, Applicants respectfully request that this rejection be withdrawn as the presently claimed invention clearly teaches how to make and use EGFR antagonists in the treatment of psoriasis.

The specification teaches those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. An EGFR/HER1 antagonist is well defined. According to the present invention, an EGFR antagonist is defined as any molecule that inhibits the stimulation of EGFR by an EGFR ligand (*see*, Specification, p. 4, ll. 25-26). Examples of EGFR antagonists include, but are not limited to, biological molecules such as antibodies (*see*, Specification, p. 5, ll. 13-28 and p. 10, ll. 10-16). Clearly, the chimeric monoclonal antibody C225 (cetuximab) is representative of EGFR/HER1 antagonists within the scope of the claimed invention. In addition, one of skill in the art would be able to determine additional antagonist using phosphorylation assays incorporated in the present disclosure (*see*, Specification, p. 5, ll. 7-12). As such, the present disclosure provides enablement commensurate in scope with the amended claims.

Moreover, the Office inappropriately cites Dillman *et al.* (J. Clin. Oncol., 1994, 12:1407-1515) and Dermer (BioTechnology, 1994, 12:320) to establish that the art of *in vivo* treatment using antibodies is complex and unpredictable. These articles address extrapolating *in vivo* results from *in vitro* experiments. Applicant would like to point out that the present invention provides human *in vivo* experimental results to enable the present claims. This clearly cannot be analogized to use of *in vitro* data to support *in vivo* claims.

Accordingly, Applicant respectfully requests the rejection be withdrawn.

2. Rejection under 35 U.S.C. § 103

Claims 1-3 and 6-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bassat *et al.* (Curr. Pharma. Design, 2000 , 6:933-942), in view of Varani *et al.* (Pathobiol., 1998, 66:253-259). In addition, claims 1-7 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Varani *et al.* (Pathobiol. 1998 66:253-259), in view of Goldstein *et al.* (WO 96/40210).

Applicant respectfully traverses the rejections and maintains that a *prima facie* case of obviousness has not been established over Bassat *et al.*, in view of Varani *et al.* To establish a *prima facie* case of obviousness, three basic criteria must be met (see M.P.E.P. § 2143). The Office has not met these three basic criteria and has instead simply provided a general incentive to combine these prior art references in view of the present disclosure to treat psoriasis using anti-EGFR antibodies. Applicant submits that neither of these references, even when combined, teaches or suggest systemic treatment of psoriasis.

The reference of Bassat *et al.* in combination with that of Varani *et al.* does not teach each and every one of the claim limitations in the present application. The Office concedes that Bassat *et al.* does not teach administering an anti-EGFR antibody as the EGFR antagonist. However, the Office asserts that Applicant would be motivated to combine the method of treating psoriasis in human patients by administering an anti-EGFR antagonist as taught by Bassat *et al.*, and the anti-EGFR antibody as taught by *in-vitro* studies of Varani *et al.* with a reasonable expectation of success. Bassat *et al.* does not, however, envision systemic administration of EGFR antagonist, much less an antibody directed against EGFR.

Bassat *et al.* teaches the use of smal molecule antagonists that inhibit protein tyrosine kinases in the treatment of psoriasi . Of the eight compounds disclosed for the three groups of tyrphostins, Bassat *et al.* ind icates that only one compound (SU 5271) is a strong candidate as an anti-psoriatic agent ( ee Bassat *et al.*, p. 939, left column, ll. 18-22). This compound is said to have "penetr ated human cadaver skin and reached the target tissue (epidermis) within 24 hours of application" indicating that the preferred mode of administration is via topical applic tion to the area of the affected skin.

Varani's paper concerns the *in-vitro* establishment of organ cultures from psoriatic lesions. Although Varani *et al.* shows that administration of EGFR antibody partially ameliorated the abnormal histological featu es of psoriatic tissues in organ, there is no evidence that systemic administration of the antibody for the treatment of psoriasis is contemplated.

Accordingly, Applicant respectfully requests the rejection be withdrawn.

Similarly, Applicant respectfully tra erses the rejection and maintains that a *prima facie* case of obviousness has not bee n established over Varani *et al.* (Pathobiol. 1998 66:253-259), in view of Goldstein *et al.* (WO 96/40210). The Office alleges that it would have been obvious to one of ordinary skill in the art to treat psoriasis using the humanized anti-EGFR antibody, C225 disc osed by Goldstein *et al.* using methods taught by Varani *et al.* Again, Applicant submits t at neither of these references, even when combined, teaches or suggest <u>systemic</u> treat ment of psoriasis.

Goldstein *et al.* discloses the use of himerized and humanized anti-EGFR antibody for treatment of cancers and not fo non-cancerous hyper-proliferative disease such as psoriasis. Varani *et al.* does not all de to any methods for treating psoriasis in humans and certainly not <u>systemic</u> administ ration of an EGFR antibody. When combined, the prior art disclosures do not te ach each and every claim limitation in the present invention. Moreover, one of ordina y skill in the art would not consid r treatment

of psoriasis using an antibody directed against growth factor receptors, such as EGFR, to have a reasonable expectation for success.

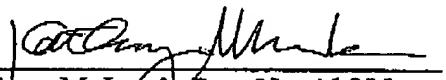
Accordingly, Applicant respectfully requests the rejection be withdrawn.

## III. CONCLUSION

Applicant believes that the present application is in condition for allowance, and respectfully requests that the Office pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

The Office is authorized to charge any fees that may be necessary for consideration of this paper to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

In the Claims:

1. (Amended) A method of treating a mammal with [a] psoriasis, [hyperproliferative disease stimulated by a ligand of a member of the epidermal growth factor family of receptors, said method] comprising systemically administering to said mammal an amount of [an antibody or a defective receptor that is] an EGFR/HER1 antagonist [of a member of the EGF family of receptors], effective to treat psoriasis.

2. (Amended) A method according to claim 1 wherein the EGFR/HER1 antagonist [of a member of the EGF family of receptor] is an antibody.

3. (Amended) A method according to claim 2 [1] wherein the antibody is a monoclonal antibody specific for EGFR/HER1 or a fragment that comprises the hypervariable region thereof.

6. (Amended) A method according to claim 1 wherein the disease is stimulated by a ligand of a member of the EGFR/HER1, said ligand is TGF-α.

8. (New) A method according to claim 1 wherein the EGFR/HER1 antagonist is a defective receptor.

## PENDING CLAIMS

1. A method of treating a mammal with psoriasis, comprising systemically administering to said mammal an amount of an EGFR/HER1 antagonist, effective to treat psoriasis.

2. A method according to claim 1 wherein the EGFR/HER1 antagonist is an antibody.

3. A method according to claim 2 wherein the antibody is a monoclonal antibody specific for EGFR/HER1 or a fragment that comprises the hypervariable region thereof.

4. A method of claim 3 wherein the monoclonal antibody is chimerized or humanized.

5. A method according to claim 3 wherein the monoclonal antibody inhibits EGFR/HER1 phosphorylation.

8. A method according to claim 1 wherein the EGFR/HER1 antagonist is a defective receptor.